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L6: Entry 1 of 21 File: USPT

DOCUMENT-IDENTIFIER: US 6335316 B1
TITLE: Method for administering acylated insulin

Brief Summary Text (13):
The present invention is a method for administering long-acting, soluble insulin by inhalation. The invention also encompasses the use of a fatty acid-acylated human insulin or a fatty acid-acylated insulin analog in the manufacture of a medicament for the treatment of diabetes or hyperglycemia by inhalation, which treatment comprises administering to a patient in need thereof an effective amount of the medicament using an inhalation device, such that the medicament is deposited in the lungs of the patient. The present invention solves two problems currently not addressed by the art. First, previous pulmonary methods for delivering insulin do not provide adequate time action to control blood glucose between meals and overnight. Second, presently known soluble, long-acting insulins and insulin derivatives are delivered by subcutaneous injection, which involves the inconvenience of preparing a sample for injection, and the pain of a needle-stick. According to the present invention, a patient in need of insulin to control blood glucose levels will achieve advantageous slow uptake and prolonged persistence in the blood of-acylated insulin compared to inhalation of non-acylated insulin, and reduced inconvenience and pain compared with subcutaneous delivery. Preferably, the acylated insulin is delivered to the lower airway of the patient. The acylated insulin can be delivered in a carrier, as a solution or suspension, or as a dry powder, using any of a variety of devices suitable for administration by inhalation. The acylated insulin can be administered using an inhalation device such as a nebulizer, a metered-dose inhaler, a dry powder inhaler, a sprayer, and the like. Preferably, the acylated insulin is delivered-in a particle size effective for reaching the lower airways of the lung, preferably less than about 10 microns mass median aerodynamic diameter (MMAD), preferably about 1 to about 5 microns MMAD, and more preferably about 1 to about 3 microns MMAD or from about 1 to about 2 microns MMAD, and most preferably from about 2 to about 3 microns MMAD. Preferred acylated insulins include a fatty acid-acylated insulin and a fatty acid-acylated insulin analog. The invention also provides a method for administering acylated insulin or acylated insulin analog together with insulin or insulin analog to a patient in need thereof by inhalation. Administering such combinations of acylated and un-acylated insulins provides both post-prandial and basal control of blood glucose levels. Because the method avoids injections, patient comfort is improved, and patient compliance increased compared with conventional insulin delivery methods.

Brief Summary Text (37):
In addition, the inhalation device must be practical, in the sense of being easy to use, small enough to carry conveniently, capable of providing multiple doses, and durable. Some specific examples of commercially available inhalation devices suitable for the practice of this invention are Turbohaler (Astra), Rotahaler (Glaxo), Diskus (Glaxo), the Ultravent nebulizer (Mallinckrodt), the Acorn II nebulizer (Marquest Medical Products) the Ventolin metered dose inhaler (Glaxo), the Spinhaler powder inhaler (Fisons), or the like. Fatty acid-acylated insulin proteins can be advantageously delivered by a dry powder inhaler or a sprayer. There are several desirable features of a dry powder inhalation device for administering fatty acid-acylated insulin protein. For example, delivery by such inhalation devices is advantageously reliable, reproducible, and accurate.

Brief Summary Text (41):
Formulations of fatty acid-acylated insulin protein for administration from a dry powder inhaler typically include a finely divided dry powder containing fatty acid-acylated insulin protein, but the powder can also include a non-acylated insulin or insulin analog to provide relatively rapid onset, and short duration of action, a bulking agent, buffer, carrier, excipient, another additive, or the like. Additives can be included in a dry powder formulation of fatty acid-acylated insulin protein, for example, to dilute the powder as required for delivery from the particular powder inhaler, to facilitate processing of the formulation, to provide advantageous powder properties to the formulation, to facilitate dispersion of the powder from the inhalation device, to stabilize to the formulation (e.g., antioxidants or buffers), to provide taste to the formulation, or the like.